False-positive Results Obtained for Immunoglobulin M Antibody Tests of Cerebrospinal Fluid for Herpes Simplex Virus in a Patient with Varicella Zoster Virus Encephalitis

Ryuta Kinno, Shinji Kurokawa, Masanobu Uchiyama, Yoshiki Sakae, Hideyo Kasai, Hiroaki Ogata and Eriko Kinugasa

Abstract

A 66-year-old man presented with a disturbed consciousness and seizure-like movements, followed by the initial symptoms of herpes zoster. Immunoglobulin (Ig) M antibodies to varicella zoster virus (VZV) as well as herpes simplex virus (HSV) were positive in the cerebrospinal fluid (CSF), whereas polymerase chain reaction of the CSF was positive for VZV-DNA but negative for HSV-DNA. The serum/CSF IgM ratio for VZV and HSV increased in association with a clinical improvement. This is a case report of a rare case of VZV encephalitis demonstrating false-positive results for IgM to HSV in the CSF. The increase in the serum/CSF IgM ratio possibly reflects a recovery from blood-brain barrier breakdown.

Key words: encephalitis, immunoglobulin M, cerebrospinal fluid, varicella zoster virus, herpes simplex virus, false-positive

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Introduction

The detection of antibodies in the cerebrospinal fluid (CSF) is a helpful diagnostic finding in some patients with encephalitis. Specific anti-viral immunoglobulin (Ig) M is often produced within a few days of primary infection and can be measured using an IgM enzyme immunoassay (EIA) (1). The sensitivity and specificity of EIA are affected by a number of factors, and false-positive results are therefore frequently observed in serum samples (2, 3). IgM antibodies do not readily diffuse across the blood-brain barrier (BBB) because of their size, and the presence of virus-specific IgM in the CSF is thus usually indicative of a central nervous system disease (4). Therefore, false-positive results obtained for IgM antibody tests in the CSF have not been described in the previous literature. We herein report the rare case of a patient with varicella zoster virus (VZV) encephalitis demonstrating false-positive results for IgM to herpes simplex virus (HSV) in the CSF. The serum/CSF IgM ratio showed notable increases correlating with a clinical improvement, possibly reflecting a recovery from BBB breakdown.

Case Report

A 66-year-old man had a fever and lower back pain and visited the pain clinic at our hospital. He had noticed blister formation on the skin of his buttocks eight days after the onset of lower back pain. He consulted a dermatologist at our hospital one day after the onset of blister formation and was subsequently diagnosed with herpes zoster in the sacral area and received treatment with oral valacyclovir at a dose of 250 mg per day. Two days after the onset of blister formation, the patient progressively presented with inappropriately speech with a disturbed consciousness; thus, he consulted our department (day 0). He had a history of IgA nephropathy with maintenance hemodialysis (three times per week). On admission to our department, his temperature was 37.5°C. He had a pulse of 81 beats per minute and a blood pressure of 106/76 mmHg. The findings of a general examination were normal, and the Glasgow Coma Score (GCS)
was 12; the eye opening, verbal response and motor response scores were 4, 3 and 5, respectively (E4V3M5). His verbal production and auditory comprehension were partially preserved. However, a neuropsychological assessment could not be performed due to his disturbed consciousness; therefore, it was difficult to determine whether his inappropriate speech was a result of disturbed consciousness or aphasia. A cranial nerve examination revealed no abnormalities. The patient showed seizure-like movements of the right arm. However, no evidence of meningeal signs was observed, and the tendon reflexes were normal. No signs of sensory, bladder or rectal disturbances were observed.

Regarding the blood tests performed on a nondialytic day, we noted a decrease in the hemoglobin level (8.3 g/dL) and increases in the blood urea nitrogen (43.4 mg/dL), creatinine (7.68 mg/dL), potassium (5.5 mEq/L) and C-reactive protein (2.15 mg/dL) levels. A CSF examination showed that the cell count had increased to 150/μL (98% lymphocytes) and the protein level had increased to 1,463 mg/dL, with a normal glucose level (80 mg/dL). The IgG index was 0.55 (cut-off: 0.7), with a CSF-serum IgG ratio of 123/791 mg/dL and albumin ratio of 1,010/3,600 mg/dL. Both oligoclonal IgG bands and myelin basic proteins were negative. Brain magnetic resonance imaging (MRI) performed on day 3 showed increased periventricular signals on both T2-weighted image (T2WI) and fluid-attenuation inversion recovery (FLAIR) images (Fig. 1A). Contrast-enhanced MRI was not performed because of the patient’s chronic renal failure. An electroencephalogram (EEG) obtained on day 1 showed slow-wave abnormalities (2-4 Hz polymorphic delta and theta activity) without epileptic activity (Fig. 1B).

Intravenous acyclovir treatment (250 mg after each dialysis, i.e., three times per week) was initiated for possible VZV encephalitis from day 0. No anti-VZV IgM antibodies were detected in the CSF according to the EIA method, whereas the patient tested positive for anti-HSV IgM antibodies (Table). The serum/CSF IgM ratio was 0.52 for VZV and 1.19 for HSV (Fig. 2). The serum/CSF IgG ratio was 38.23 for VZV and 9.10 for HSV (see Table for each serum and CSF IgG value). On day 5, IgM antibodies to VZV were detected in the CSF. The serum/CSF IgM ratio was 0.56 for VZV and 1.28 for HSV, and the serum/CSF IgG ra-
The current patient presented with a disturbed consciousness and seizure-like movements, followed by the initial symptoms of herpes zoster in the sacral area, such as fever and lower back pain. A CSF examination revealed an elevated cell count, with a normal glucose level. Brain MRI showed multiple periventricular lesions, and the patient’s EEG showed slow-wave abnormalities, indicating encephalitis. PCR for VZV-DNA in the CSF was positive. These clinical features are compatible with VZV encephalitis (5). He had received oral valacyclovir and had a past history of chronic renal failure before the onset of disturbed consciousness, suggesting the possibility of valacyclovir neurotoxicity (VAN). While the symptoms of VAN usually appear within the first 72 hours of treatment, the average time between dermatological and neurological symptoms is approximately one week for VZV encephalitis (6). The presence of inflammatory cells in the CSF and detection of MRI abnormalities also suggest VZV encephalitis (7). Taking these findings together, the possibility of VAN was negative in our case. It was notable that IgM antibodies to both HSV and VZV were detected in the CSF, possibly reflecting dual infection of the central nervous system caused by both viruses. It is recommended that PCR-based analyses of the CSF be repeated after a few days, because PCR can sometimes be negative if the sample is obtained early in the illness (1). Two CSF samples in this case tested negative for HSV-DNA on PCR, suggesting false-positive results for anti-HSV IgM antibodies in the CSF.

To our knowledge, this is the first report of false-positive results for anti-HSV IgM antibody tests of the CSF. The presence of IgG antibodies to several viruses in the CSF may suggest BBB breakdown (8). In the current case, IgG

### Table. Virological Findings.

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 19</th>
<th>Day 25</th>
<th>Day 32</th>
<th>Day 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV-IgG (0.4)</td>
<td>0.17</td>
<td>6.26</td>
<td>9.04</td>
<td>≥12.60</td>
<td>12.97</td>
<td>≥12.60</td>
</tr>
<tr>
<td>VZV-IgM (1.2)</td>
<td>0.46</td>
<td>4.82</td>
<td>1.18</td>
<td>0.85</td>
<td>1.54</td>
<td>0.32</td>
</tr>
<tr>
<td>HSV-IgG (0.4)</td>
<td>7.11</td>
<td>8.69</td>
<td>4.45</td>
<td>6.16</td>
<td>6.14</td>
<td>4.67</td>
</tr>
<tr>
<td>HSV-IgM (1.2)</td>
<td>2.01</td>
<td>1.84</td>
<td>0.90</td>
<td>0.94</td>
<td>1.09</td>
<td>0.62</td>
</tr>
<tr>
<td>VZV-DNA</td>
<td>9×10E4</td>
<td>9×10E4</td>
<td>≤2×10E2</td>
<td>≤2×10E2</td>
<td>≤2×10E2</td>
<td></td>
</tr>
<tr>
<td>HSV-DNA</td>
<td>≤2×10E2</td>
<td>≤2×10E2</td>
<td></td>
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Antibody index of the IgM and EIA titer for IgG assessed using EIA and the amount of DNA synthesized via PCR are shown. The numbers shown in parentheses denote cutoff values for each item.

CSF: cerebrospinal fluid, HSV: herpes simplex virus, VZV: varicella zoster virus

Figure 2. Serum/CSF IgM ratio. The serum/CSF IgM ratios were increased at approximately the same time. CSF: cerebrospinal fluid, HSV: herpes simplex virus, VZV: varicella zoster virus

![Graph showing Serum/CSF IgM ratio](image)

to was 20.16 for VZV and 7.48 for HSV. Polymerase chain reaction (PCR) for VZV-DNA in the CSF was positive on days 0 and 5, whereas PCR was negative for HSV-DNA in two CSF samples. Based on these results, the patient was diagnosed with VZV encephalitis.

The patient gradually regained consciousness, and his general condition improved after the sixth cycle of acyclovir therapy. PCR for VZV-DNA in the CSF became negative on day 25, and acyclovir was discontinued. IgM antibodies to VZV and HSV in the CSF disappeared, while IgG antibodies to VZV and HSV in the CSF were still detectable (Table). The titer of IgG antibodies to VZV in both the serum and CSF chronologically increased from day 0 to 44, while those to HSV showed an almost constant titer during the follow-up period. Both the serum/CSF IgM ratios for VZV (1.19) and HSV (2.80) were mildly increased (Fig. 2). On day 44, a CSF examination showed that the cell count had improved to 63/μL (100% lymphocytes) and that the protein level had improved to 215 mg/dL. Interestingly, both the serum/CSF IgM ratios for VZV (3.84) and HSV (4.18) were increased at approximately the same time. In order to continue rehabilitation for disuse syndrome due to prolonged immobility, the patient was transferred to the rehabilitation hospital on day 61.

### Discussion

The current patient presented with a disturbed consciousness and seizure-like movements, followed by the initial symptoms of herpes zoster in the sacral area, such as fever and lower back pain. A CSF examination revealed an elevated cell count, with a normal glucose level. Brain MRI showed multiple periventricular lesions, and the patient’s EEG showed slow-wave abnormalities, indicating encephalitis. PCR for VZV-DNA in the CSF was positive. These clinical features are compatible with VZV encephalitis (5). He had received oral valacyclovir and had a past history of chronic renal failure before the onset of disturbed consciousness, suggesting the possibility of valacyclovir neurotoxicity (VAN). While the symptoms of VAN usually appear within the first 72 hours of treatment, the average time between dermatological and neurological symptoms is approximately one week for VZV encephalitis (6). The presence of inflammatory cells in the CSF and detection of MRI abnormalities also suggest VZV encephalitis (7). Taking these findings together, the possibility of VAN was negative in our case. It was notable that IgM antibodies to both HSV and VZV were detected in the CSF, possibly reflecting dual infection of the central nervous system caused by both viruses. It is recommended that PCR-based analyses of the CSF be repeated after a few days, because PCR can sometimes be negative if the sample is obtained early in the illness (1). Two CSF samples in this case tested negative for HSV-DNA on PCR, suggesting false-positive results for anti-HSV IgM antibodies in the CSF.

To our knowledge, this is the first report of false-positive results for anti-HSV IgM antibody tests of the CSF. The presence of IgG antibodies to several viruses in the CSF may suggest BBB breakdown (8). In the current case, IgG
antibodies to VZV as well as HSV were present in the CSF, indicating BBB breakdown. In addition, the weakly positive reaction of serum IgM antibodies to HSV was consistently observed on all tests conducted during the follow-up period, without any apparent symptoms of HSV infection, while the serum IgM antibody titer to VZV was undetectable on day 0 (Table). Serological procedures often yield false-positive IgM results due to the reactivation of HSV without clinical relevance, polyclonal antibody synthesis, nonspecific binding and/or cross-reactions (2, 3). Such serological mechanisms may influence the serological findings in the present case. Anti-VZV IgM antibodies can be measured just 3-4 days after the development of exanthema (9). In our case, serum anti-VZV IgM antibody tests were negative two days after the onset of blister formation but positive seven days after the onset of blister formation. In addition, lower back pain presented approximately eight days before blister formation on the skin of the patient’s buttocks. These clinical features are compatible with those of previous findings. Taking these findings together, it is possible that the anti-HSV IgM antibodies were nonspecifically produced and that these IgM antibodies passed through the severely disrupted BBB. The chronologically increased titer of anti-VZV IgG antibodies with almost a constant titer of anti-HSV IgG antibodies also reflects VZV infection with nonspecific production of anti-HSV antibodies. Further research is required to understand the mechanisms underlying false-positive results for anti-viral IgM in the CSF.

We observed notable increases in the serum/CSF ratio for VZV and HSV (Fig. 2). Previous studies have suggested that a low serum/CSF IgG ratio (≤20) indicates intrathecal antibody production within the brain, whereas there is no previous evidence for the serum/CSF IgM ratio (5, 8). During the acute phase, our patient showed a low serum/CSF IgM ratio for VZV, accompanied by positive results for PCR of VZV-DNA in the CSF. During the subacute phase, both the serum/CSF IgM ratios for VZV and HSV were increased at approximately the same time. The low ratio during the acute phase could suggest intrathecal IgM antibody production, as supported by the positive results of PCR for VZV-DNA. Meanwhile, the simultaneous increases in the serum/CSF IgM ratios for VZV and HSV may reflect a recovery from BBB breakdown, as supported by the negative results of PCR for VZV-DNA. Taking these findings together, the serum/CSF IgM ratio may be an indicator of BBB abnormalities. Regarding IgG, our case showed results that were inconsistent with previous findings, such as a high serum/CSF IgG ratio for VZV (≥20) during the acute phase despite a positive PCR result, suggesting that determining the serum/CSF IgG ratio is insufficient for diagnosis during the acute phase. We thus conclude that the results for anti-viral antibody tests of the CSF should be interpreted with caution when severe BBB breakdown is assumed.

The authors state that they have no Conflict of Interest (COI).

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References


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